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Cinchona-catalysed, enantioselective synthesis of β-peroxycarboxylic acids, β-peroxyesters and β-peroxyalcohols

K. O'Reilly[a,b], M. K. Gupta[a,b], H. Gandhi[a,b], V. P. Kumar[a,b], K. S. Eccles[a,b], S. E. Lawrence[a,b] and T. P. O'Sullivan[*a,b,c]

[a]*Department of Chemistry, University College Cork, Cork, Ireland;* [b]*Analytical and Biological Chemistry Research Facility, University College Cork, Cork, Ireland;* [c]*School of Pharmacy, University College Cork, Cork, Ireland.*

Abstract: A cinchona-catalysed, enantioselective oxa-Michael reaction of α,β-unsaturated aldehydes with either *tert*-butyl hydroperoxide or cumene hydroperoxide was developed. Optimisation of reaction parameters afforded β-peroxycarboxylic acids, β-peroxyesters or β-peroxyalcohols in high yields and moderate to good enantioselectivities. These latter β-peroxyalcohols offer a direct route to 5-membered, chiral cycloperoxides.

Keywords: organocatalysis; cinchona; peroxidation; peroxyacids; peroxyesters, peroxyalcohols, cycloperoxides.

1. INTRODUCTION

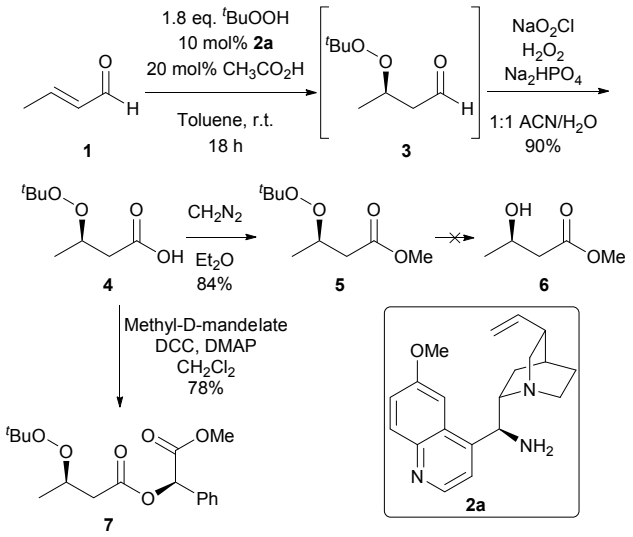
More than 600 peroxides have been isolated and characterized from a variety of plant and animals sources [1-3]. Peroxide-containing natural products are particularly common in marine sponges [4]. Among the many peroxides studied, a significant number were found to be biologically active, displaying antiparasitic, antibacterial and cytotoxic properties [5, 6]. Despite the potential of these compounds, methods for the synthesis of chiral peroxides remain relatively limited [7-11]. A major breakthrough in this field came with the discovery by Deng *et al.* of a highly enantioselective peroxidation of α,β-unsaturated ketones using a cinchona-based organocatalyst [12]. Other groups have since reported the enantioselective peroxidation of nitroalkenes [13], imines [14], and Morita-Baylis-Hillman carbonates [15]. More recently, Deng has reported the asymmetric peroxidation of α,β-unsaturated aldehydes with a focus on α-methoxydiphenyl hydroperoxide as the peroxide source [16]. In this article, we outline our parallel work on the asymmetric peroxidation of α,β-unsaturated aldehydes with both *tert*-butyl hydroperoxide (TBHP) and cumene hydroperoxide. We describe how conditions were optimized for the preparation of chiral β-peroxycarboxylic acids, β-peroxyesters and β-peroxyalcohols in high yields. Finally, we demonstrate the synthetic utility of these β-peroxyalcohols by their conversion into chiral, 5-membered cycloperoxides *via* a silver-mediated cyclisation step.

*Address correspondence to this author at the Department of Chemistry, University College Cork, Cork, Ireland; Tel/Fax: +353-21-4901655, +353-21-4901656; E-mails: tim.osullivan@ucc.ie

2. ASYMMETRIC PEROXIDATION

2.1. Catalyst screening and optimisation

Using conditions similar to those developed by Deng for the peroxidation of unsaturated ketones, we employed **2a**, which is readily prepared from quinine[17, 18], as our catalyst (Scheme 1). Addition of TBHP to crotonaldehyde in the presence of 10 mol% **2a** and 20 mol% acetic acid saw complete consumption of the starting material. However, the desired β-*tert*-butylperoxyaldehyde **3** was found to be difficult to purify *via* column chromatography although a pure sample of the unstable compound could be isolated in a low yield of 10%.



Scheme 1.

Believing that the stability of the β-*tert*-butylperoxyaldehyde was impacting on yields, we opted to instead oxidise the crude product to the corresponding β-peroxycarboxylic acid by way of a Pinnick oxidation. Gratifyingly, this approach afforded β-peroxycarboxylic acid **4** in 90% yield without need for further purification. While

Deng had determined the enantiopurity of his β-peroxyketones by their conversion to the corresponding β-hydroxyketone *via* hydrogenolysis, the peroxide group in both β-peroxycarboxylic acid **4** and β-peroxyester **5** resisted reduction even under forcing conditions. Accordingly, enantiopurity was determined by coupling of the β-peroxycarboxylic acid with methyl D-mandelate and separation of the resultant diastereomers by chiral HPLC. The absolute stereochemical configuration was determined by the fortuitous crystallisation of the minor diastereomer of mandelate ester **7**, namely (*S,R*)-**7**, from an oily mixture of both diastereomers (Figure 1). Comparison of the retention time for this compound confirmed it to be the minor diastereomer.

The choice of solvent is an important consideration in organocatalysed reactions [19, 20]. For cinchona-based catalysts in solution, the preferred conformation plays an important role in influencing reaction outcomes [21]. As cinchona alkaloids adopt diverse conformations in different solvents [22, 23], a solvent screen was next undertaken. Less polar solvents, such as toluene and hexane, resulted in lower enantioselectivities of 37% and 29% respectively. The highest selectivities were recorded with more polar solvents, with ethyl acetate affording an enantiomeric excess of 44% and an overall yield of 74%.

The nature of the acid co-catalyst has also been shown to impact on both yields and enantioselectivity. Switching from acetic acid to trifluoroacetic acid at 20 mol% loading saw no improvement, though reducing the loading to 10 mol% saw an increase in selectivity to 49% (Table 1, entries 1, 2). A comparison of other fluorine-containing organic acids showed that enantioselectivity increased with decreasing co-catalyst pKa (Table 1, entries 3-7), with the highest enantiomeric excesses of 60% being recorded with pentafluorobenzoic acid (PFBA) and tetrafluoroterephthalic acid respectively. Moving to more acidic co-catalysts led to a dramatic decrease in selectivity (Table 1, entries 8, 9).

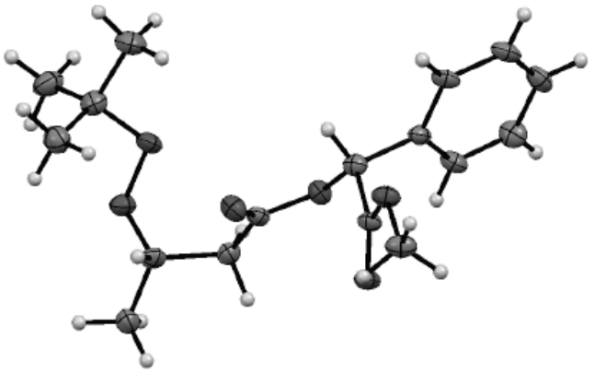
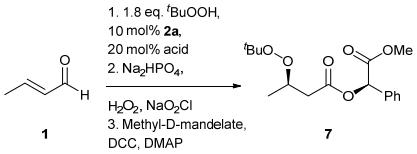


Figure 1. X-ray crystal structure of minor diastereomer (*S,R*)-**7**.

Table 1. Effect of acid co-catalyst on enantioselectivity.



Entry	Acid co-catalyst	pKa	Yield	ee
1	Trifluoroacetic acid	0.2	80%	42%
2	Trifluoroacetic acid (10 mol%)	0.2	83%	49%
3	4-Trifluoromethylbenzoic acid	3.6	72%	44%
4	2,4-Bistrifluoromethylbenzoic acid	3.3	77%	55%
5	Tetrafluorophthalic acid	1.87	67%	56%
6	Pentafluorobenzoic acid	1.48	74%	60%
7	Tetrafluoroterephthalic acid	1.17	75%	60%
8	Perfluorobutyric acid	0.4	58%	21%
9	Methanesulfonic acid	-1.9	45%	0%
10	Camphorsulfonic acid	1.2	73%	40%

Interestingly, though camphorsulfonic acid has a similar pKa to tetrafluoroterephthalic acid, the non-fluorinated co-catalyst afforded significantly poorer selectivities (Table 1, entry 10). In subsequent studies, we decided to employ PFBA as our preferred acid co-catalyst, as it gave comparable ee's to terafluoroterephthalic acid but is considerably less expensive.

Having investigated the reaction conditions, we next turned our attention to derivatising catalyst **2a**. The cinchona alkaloid skeleton is easily modified and these modifications have a proven track record in the field of organocatalysis. For example, conversion of the 9-NH_2 to a thiourea often results in an enhancement in both efficacy and selectivity [24]. Accordingly, a range of catalysts was prepared and tested for their ability to catalyse the asymmetric addition of TBHP to crotonaldehyde (Figure 2). The results are summarised in Table 2.

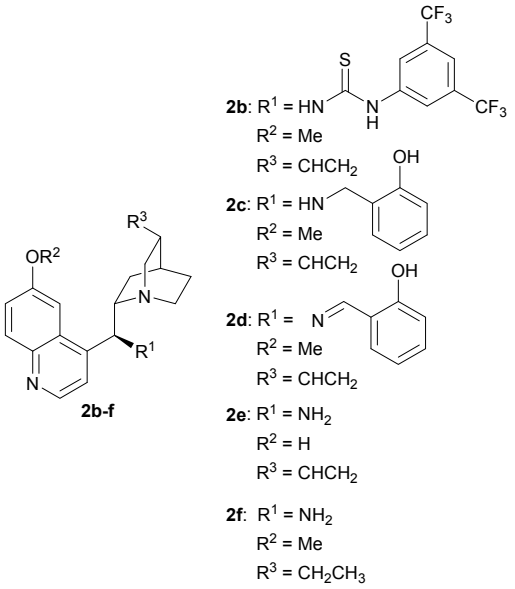
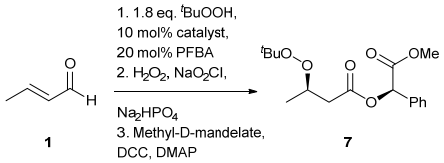


Figure 2. Modified catalysts for screening.

Table 2. Influence of catalyst on asymmetric peroxidation of crotonaldehyde.



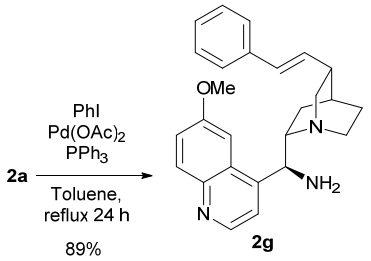
Entry	Catalyst	Yield	ee
1	**2a**	74%	60%
2	**2b**	68%	2%
3	**2c**	61%	33%
4	**2d**	57%	46%
5	Quinine	77%	0%
6	Cinchonine	81%	0%
7	**2e**	59%	40%
8	**2f**	76%	52%
9	**2g**	75%	58%

Use of thiourea derivative **2b** [25] did afford the desired target in 68% yield but was accompanied by almost complete loss of enantioselectivity (Table 2, entry 2). Other modifications of the 9-NH_2 group, such as secondary amine **2c** and Schiff base **2d** developed by He [26], afforded higher enantioselectivites of 33% and 46% respectively (Table **2**, entries 3, 4). Interestingly, He also found that the Schiff base was superior to the secondary amine in his studies on asymmetric Henry reactions.

While the primary amine proved crucial for enantioselectivity, it was not a prequisite for activity, with both quinine and cinchonine providing the target compound in high yields, albeit as racemic mixtures (Table 2, entries 5,6). These results suggest that pathways other than the iminium ion/peroxyenamine catalytic cycle previously proposed may be at play [12].

Demethylation of the aromatic methoxy group introduces an additional acidic, H-bonding site which potentially provides an additional site for interaction between catalyst **2e** [27] and the substrate. However, **2e** was found to demonstrate poorer activity and selectivity relative to **2a** in our system (Table 2, entry 7).

Reduction of the olefinic bond in **2a** may also lead to improvements, as in the asymmetric reflexive-Michael reaction of ynones with aldehydes and indane-1,3-dione [28]. However, asymmetric peroxidation of crotonaldehyde with **2f** was less selective than with **2a** (Table 2, entry 8). Introduction of bulky groups into the terminal alkene moiety might reasonably be expected to impact on catalyst conformation and hence, activity. Accordingly, catalyst **2g** was prepared in 89% yield *via* a Heck reaction between **2a** and iodobenzene (Scheme 2). **2g** was found to be comparable with **2a** in terms of yields and enantioselectivity (Table 2, entry 9). As none of the catalysts screened displayed improved performance over our original catalyst, we decided to next investigate the substrate scope of **2a**.

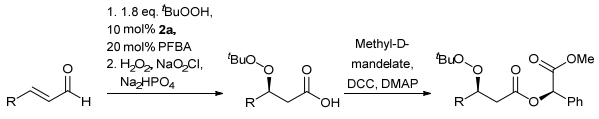


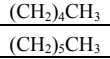
Scheme 2.

2.2. Substrate scope and application

A range of aliphatic, α,β-unsaturated aldehydes, from four to twelve carbons in length, was subjected to our optimised conditions with TBHP as the peroxide source. The desired β-peroxycarboxylic acids were isolated in excellent yields without need for further purification (Table 3, entries 1-9). While yields were consistently good, epoxidation did become increasingly noticeable as chain length increased. However, reducing the reaction temperature to 4°C blocked this epoxidation side reaction. Enantiomeric excesses were determined by conversion to the corresponding mandelate ester and ranged from 60% to 68% with a preference for formation of the (*R*)-isomer across the aldehydes tested. No discernible relationship between chain length and stereoselectivity was evident. While conjugated, aromatic α,β-unsaturated aldehydes did not react under these conditions (Table 3, entry 10), non-conjugated, aromatic substrates were amenable to asymmetric peroxidation, with the target peroxide produced in 78% yield and 66% ee (Table 3, entry 11). Peroxidation was also found to be regioselective, with reaction occurring only at the conjugated olefinic bond (Table 3, entry 12).

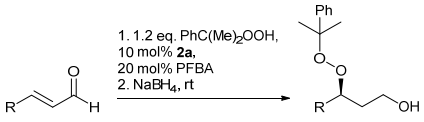
Table 3. Synthesis of β-*t*-butylperoxyacids and β-*t*-butylperoxyesters



Entry	R	Acid yield	Ester yield	ee
1	CH_3	90%	82%	60%
2	CH_2CH_3	91%	79%	63%
3	$(CH_2)_2CH_3$	87%	82%	66%
4	$(CH_2)_3CH_3$	89%	84%	68%
5	$(CH_2)_4CH_3$	92%	78%	65%
6	$(CH_2)_5CH_3$	86%	75%	66%
7	$(CH_2)_6CH_3$	88%	81%	65%
8	$(CH_2)_7CH_3$	94%	83%	64%
9	$(CH_2)_8CH_3$	94%	86%	66%
10	Ph	n.r.	-	-
11	$(CH_2)_2Ph$	77%	78%	66%
12		71%	81%	67%

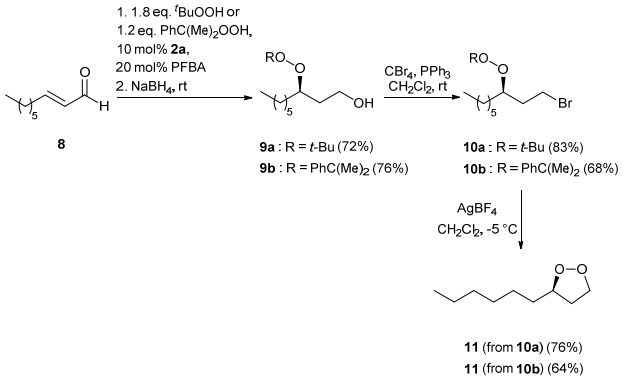
Other peroxide sources, such as cumene hydroperoxide, may also be employed. As the cumyl group contains a good chromophore, the degree of enantioselectivity was determined by sodium borohydride-mediated reduction of the β-peroxyaldehydes to the stable β-peroxyalcohols and separation of the resultant enantiomers by chiral HPLC. The β-peroxyalcohols were obtained in good to excellent yields of 76-84% from a range of aldehyde substrates (Table 4, entries 1-9). We observed, similar to Deng, that the degree of selectivity was dependent on the peroxide source and that cumene hydroperoxide afforded lower enantioselectivies than TBHP with ee's ranging from 55% to 66%. While Deng's work focusses primarily on α-methoxydiphenyl hydroperoxide, he did record the peroxidation of 1-nonenal with cumene hydroperoxide in 72% ee and with 70% conversion as determined by ^{1}H-NMR. Using our methodology, we recorded a comparable enantiomeric excess of 64% with the same substrate and successfully isolated the corresponding β-peroxyalcohol in a yield of 76% (Table 4, entry 6).

Table 4. Asymmetric peroxidation with cumene hydroperoxide.



Entry	R	Yield	ee
1	CH_3	83%	56%
2	CH_2CH_3	81%	64%
3	$(CH_2)_2CH_3$	77%	62%
4	$(CH_2)_3CH_3$	84%	66%
5	$(CH_2)_4CH_3$	82%	59%
6	$(CH_2)_5CH_3$	76%	64%
7	$(CH_2)_6CH_3$	78%	58%
8	$(CH_2)_7CH_3$	84%	65%
9	$(CH_2)_8CH_3$	80%	55%

The synthetic utility of the β-peroxyalcohols lies in their ability to be transformed into chiral, 5-membered cycloperoxides. Alcohols **9a-b** were readily converted to the corresponding primary alkyl bromides **10a-b** using a combination of carbon tetrabromide and triphenylphosphine (Scheme 3). Treatment of these alkyl bromides with silver tetrafluoroborate furnished 1,2-dioxolane **11** in either 76% yield from *tert*-butylperoxyalkyl bromide **10a** or in a slightly lower yield of 64% from cumylperoxyalkyl bromide **10b**. The reaction proceeds by trapping of the oxygen lone pair by the incipent carbocation followed by loss of the *tert*-butyl or cumyl group and formation of the cycloperoxide product [29].



Scheme 3.

CONCLUSION

In summary, we have developed a methodology for the asymmetric peroxidation of α,β-unsaturated aldehydes with either *tert*-butyl hydroperoxide and cumene hydroperoxide using a modified quinine catalyst with moderate to good enantioselectivites. We have also described how the resultant, unstable β-peroxyaldehydes can be readily converted to stable β-peroxycarboxylic acids, β-peroxyesters and β-peroxyalcohols in high yields. Finally, we have demonstrated that these β-peroxyalcohols offer a direct route to 1,2-dioxolanes.

CONFLICT OF INTEREST

KOR and HG thank the Irish Research Council for funding. The research leading to these results has received funding from the People Programme (Marie Sklodowska Curie Actions) under REA grant agreements 272194 (MKG) and 655508 (VPK). The authors confirm that this article content has no conflicts of interest.

ACKNOWLEDGEMENTS

Declared none.

SUPPLEMENTARY MATERIAL

Full experimental details as well as spectroscopic characterisation data is available in the SI.

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